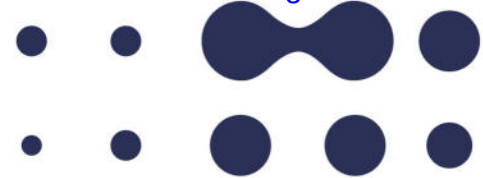


# Exhibit 4



5 July 2024

## *IARC Monographs* evaluate the carcinogenicity of talc and acrylonitrile *IARC Monographs* Volume 136

### Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 136: Talc and Acrylonitrile, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place on 11–18 June 2024.

The Working Group of 29 [international experts](#) from 13 countries evaluated the carcinogenicity of talc and acrylonitrile.

More information about Meeting 136 is available on the *IARC Monographs* website:  
<https://monographs.iarc.who.int/iarc-monographs-volume-136/>.

The outcome of the assessment has been published in a summary article in *The Lancet Oncology*<sup>1</sup> and will be described in detail in Volume 136 of the *IARC Monographs*, to be published in 2025.

**Table 1. Summary of classifications in *IARC Monographs* Volume 136**

| Agent         | Evidence stream  |                                |  | Overall evaluation |
|---------------|--|--------------------------------|--|--------------------|
|               | Cancer in humans   | Cancer in experimental animals | Mechanistic evidence (key characteristics of carcinogens)  |                    |
| Acrylonitrile | <i>Sufficient</i> evidence (lung cancer)<br><i>Limited</i> evidence (bladder cancer) | <i>Sufficient</i> evidence     | <i>Strong</i> mechanistic evidence in experimental systems   | Group 1            |
| Talc          | <i>Limited</i> evidence (ovarian cancer)   | <i>Sufficient</i> evidence     | <i>Strong</i> mechanistic evidence of key characteristics of carcinogens in human primary cells and experimental systems | Group 2A           |

<sup>1</sup> Stayner L, Carreón-Valencia T, Demers P, Fritz J, Sim M, Stewart P, et al. (2024). Carcinogenicity of talc and acrylonitrile. *Lancet Oncol*. Published online 5 July 2024; [https://doi.org/10.1016/S1470-2045\(24\)00384-X](https://doi.org/10.1016/S1470-2045(24)00384-X)



## ACRYLONITRILE

### 1. How is acrylonitrile used?

**Acrylonitrile** (CAS No. 107-13-1) is a volatile organic compound that is mainly used in the production of polymers. These include the homopolymer polyacrylonitrile and several important copolymers, such as styrene–acrylonitrile, acrylonitrile butadiene styrene, and synthetic rubbers such as acrylonitrile butadiene. Uses of these polymers include synthetic fibres for clothing, carpets, and other textiles, as well as plastics for consumer products, automotive parts, and construction.

### 2. Who is exposed to acrylonitrile?

Occupational exposure may occur in the production of acrylonitrile and its use in polymer production. Acrylonitrile is present in cigarette smoke. The general population is exposed to acrylonitrile mainly via cigarette smoke, including passive smoking (second-hand smoke). Another source of exposure is air pollution. Several acrylonitrile metabolites and adducts have been measured as biomarkers of exposure to acrylonitrile.

### 3. How did the Working Group arrive at its classification of acrylonitrile?

The Working Group classified acrylonitrile as *carcinogenic to humans* (Group 1) on the basis of *sufficient* evidence for cancer in humans for lung cancer. There was also *limited* evidence in humans for bladder cancer.

In experimental animals, there was *sufficient* evidence for cancer. Acrylonitrile caused an increase in the incidence of malignant neoplasms in both sexes of two species in multiple studies, including one study that complied with Good Laboratory Practice. Finally, there was *strong* mechanistic evidence of key characteristics of carcinogens (KCs) in experimental systems.

Acrylonitrile is electrophilic or is metabolically activated to an electrophile (KC1), is genotoxic (KC2), induces oxidative stress (KC5), causes immortalization (KC9), and alters cell proliferation, cell death, or nutrient supply (KC10). Acrylonitrile is metabolized to electrophiles that can bind to DNA or RNA and various proteins. It induces genetic alterations, including mutations in many different species from bacteria to rodents. In several studies in vivo and in vitro, acrylonitrile was found to induce generation of reactive oxygen species and oxidative damage to DNA, and to alter levels of antioxidant proteins. In addition, acrylonitrile causes immortalization and cell transformation and promotes cell proliferation. Hyperplasia was observed in rodents.

### 4. Has acrylonitrile been previously evaluated?

**Acrylonitrile** was evaluated by the *IARC Monographs* programme in 1998<sup>2</sup> as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient* evidence for cancer in experimental animals.

<sup>2</sup> IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part 1, Part 2, Part 3). *IARC Monogr Eval Carcinog Risks Hum.* 71:1–1586. Available from: <https://publications.iarc.who.int/89> PMID:10507919.



Acrylonitrile is listed by the Organisation for Economic Co-operation and Development (OECD) (for 2007) and the United States Environmental Protection Agency (US EPA) as a chemical with a high production volume.

#### 5. Why was acrylonitrile re-evaluated?

Acrylonitrile was accorded high priority for evaluation by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024.<sup>3</sup>

This recommendation was based on the availability of new evidence from epidemiological studies of cancer in humans, including studies able to control for smoking, and mechanistic evidence of genotoxicity and oxidative stress.

#### 6. What types of exposures and cancer sites were reviewed by the Working Group?

For acrylonitrile, all of the studies except one evaluated occupational exposure to acrylonitrile in industries that use or produce acrylonitrile. One study evaluated acrylonitrile metabolites that resulted from smoking and their association with oesophageal cancer, in the general population.

The strongest evidence came from a large cohort study of workers in different industries producing or using acrylonitrile. In this study, workers with higher exposure to acrylonitrile had a higher rate of lung cancer mortality compared with workers with lower exposures. The study performed several additional analyses to rule out biases, and the increased rate of lung cancer was observed in all of those analyses.

There was also a large case–control study reporting a higher chance of prior exposure to acrylonitrile in lung cancer cases than in controls who did not have lung cancer. Several other smaller cohort studies also provided evidence indicating a higher rate of lung cancer in workers with higher exposure to acrylonitrile.

For bladder cancer, the increased rate was observed only in some of the analyses in the large study, and the body of evidence was less consistent.

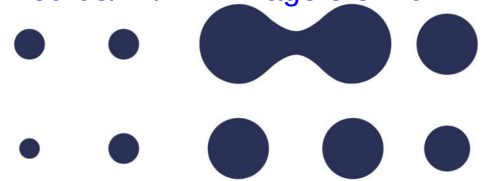
### TALC

#### 7. How is talc used?

**Talc** (CAS No. 14807-96-6), a naturally occurring mineral, is mined in many regions worldwide. It has also been synthesized, but the use of synthetic talc is minimal.

Talc is used as an anti-caking agent and lubricant in animal feed and fertilizers, as a source of magnesium and silicon in the production of ceramics, and as a coating agent or filler in foods. Talc is used in the production of rubber, plastics, paints and coatings, and some building materials. For paper, it is used as a filler and to improve

<sup>3</sup> IARC (2019). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: [https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities\\_2020-2024.pdf](https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf).



surface properties. Talc is used in drugs and as a sclerosing agent in pleurodesis. Talc-based body powders have been used widely either as baby powders to prevent diaper dermatitis or as adult body powders to absorb sweat and odours.

#### 8. What type of talc was evaluated by the Working Group?

The agent evaluated for this volume is talc, which includes both naturally occurring mineral talc and synthetic talc. This evaluation applies to lamellar and fibrous talc forms, including asbestiform talc. Asbestiform talc is not asbestos but is a type of fibrous talc. However, talc (fibrous or not) may be contaminated with asbestos.

Talc is listed by the Organisation for Economic Co-operation and Development (OECD) (for 2007) and the United States Environmental Protection Agency (US EPA) as a mineral with a high production volume.

#### 9. How did the Working Group arrive at its classification of talc?

The Working Group classified talc as *probably carcinogenic to humans* (Group 2A) on the basis of a combination of *limited* evidence for cancer in humans (for **ovarian cancer**), *sufficient* evidence for cancer in experimental animals, and *strong* mechanistic evidence that talc exhibits key characteristics of carcinogens in human primary cells and experimental systems.

There were numerous cancer studies in humans that consistently showed an increase in the incidence of ovarian cancer among women reporting use of body powder in the perineal region. However, the Working Group concluded that a causal association could not be fully established because the increase could potentially be explained by contamination of the talc with asbestos (which has been documented) or by biases arising from the studies' methodology.

An assessment of biases by the Working Group led to the conclusion that a positive association between talc use and ovarian cancer was observed, but that different reporting of talc use by study participants who had cancer and those who did not have cancer could not be entirely ruled out.

There were also increased rates of ovarian cancer in studies of women working in the pulp and paper industry, which entails exposure to talc. However, confounding by co-exposure to asbestos could not be excluded, and the increased rates were based on small numbers of ovarian cancers in those occupational studies.

#### 10. Can you tell us a bit more about talc in experimental animals?

**In experimental animals**, treatment with talc caused an increase in the incidence of malignant neoplasms in females (adrenal medulla and lung) and a combination of benign and malignant neoplasms in males (adrenal medulla) of a single species (rat). The rationale for *sufficient* evidence included the unusual tumour types reported in this study (i.e. pheochromocytomas and adrenal tumours after exposure to talc by inhalation), that pheochromocytoma (especially malignant pheochromocytoma) of the adrenal medulla is a rare lesion, and that tumours were observed in both sexes in a high-quality study conducted under Good Laboratory Practice.



### 11. What about mechanistic evidence?

In several different types of experimental system, talc induced chronic inflammation in various tissues after administration via different routes and exposures for up to 2 years. In addition, end-points associated with cell proliferation and cell growth were observed in human primary cells, and hyperplasia was observed in the respiratory system of rodents exposed chronically by inhalation or acutely by intratracheal administration. These evaluations of experimental evidence focused on studies in which it was highly unlikely that the talc was contaminated with asbestos.

### 12. Has talc been evaluated previously?

Talc containing asbestos is currently classified as *carcinogenic to humans* (Group 1), as part of the classification of asbestos carried out in *IARC Monographs* Volume 100C.<sup>4</sup> There is *sufficient* evidence that asbestos causes mesothelioma and cancers of the lung, larynx, and ovary in humans. There is *limited* evidence that asbestos causes cancers of the pharynx, stomach, and colorectum.

Talc containing asbestos remains part of the definition of asbestos (classified in Group 1) and was not evaluated for this volume.

Perineal use of talc-based body powder was evaluated by the *IARC Monographs* programme in 2006 in Volume 93<sup>5</sup> as *possibly carcinogenic to humans* (Group 2B) on the basis of *limited* evidence for ovarian cancer. Inhaled talc not containing asbestos or asbestiform fibres was *not classifiable as to its carcinogenicity to humans* (Group 3).

This new evaluation of “talc” supersedes the previous evaluations of “talc not containing asbestos or asbestiform fibres” and “perineal use of talc-based body powder”.

The Working Group concluded that contamination of talc with asbestos remains a major concern and may lead to exposure of workers and the general population, including children, to asbestos (e.g. via contaminated talc-based make-up). The Working Group also noted that contamination of talc products with asbestos has been documented and that industry standards used to assess talc in cosmetic and pharmaceutical products have often not been sufficiently sensitive to rule out contamination with asbestos.

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<sup>4</sup> IARC (2012). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum.* 100C:1–501. Available from: <https://publications.iarc.who.int/120> PMID:23189751.

<sup>5</sup> IARC (2010). Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum.* 93:1–452. Available from: <https://publications.iarc.who.int/111> PMID:21449489.





### 13. Why was talc re-evaluated?

Talc was accorded high priority for evaluation by the Advisory Group to Recommend *Priorities for the IARC Monographs* during 2020–2024.<sup>6</sup>

Talc was recommended on the basis of the availability of well-designed cohort studies that evaluated cancer rates associated with exposure to talc powder, as well as new mechanistic evidence.

### 14. What types of exposures and cancer sites were reviewed by the Working Group?

The available informative studies included occupational cohorts in mining and user industries and were conducted mostly in male populations, with the exception of studies in the pulp and paper industry, which also included women. The studies in the pulp and paper industry are the only occupational cohort studies that were able to assess ovarian cancer. The other cancer outcomes explored in occupational studies are mainly respiratory and digestive cancers.

There were also numerous studies conducted in the general population. Most of these studies assessed ovarian cancer (and, to a lesser extent, cancers of other female reproductive organs, e.g. the uterus) associated with application of body powder in the perineal area. Those studies included case–control studies and cohort studies.

## IARC MONOGRAPHS EVALUATIONS

### 15. What does the *IARC Monographs* classification mean in terms of risk?

The *IARC Monographs* classification indicates the strength of the evidence that a substance or agent can cause cancer. The *IARC Monographs* programme seeks to identify cancer hazards, meaning the potential for the exposure to cause cancer. However, the classification does not indicate the level of cancer risk associated with exposure at different levels or in different scenarios. The cancer risk associated with substances or agents that are assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the size of the effect of the agent at a given exposure level.

### 16. What are the different strength-of-evidence evaluation groups used by the *IARC Monographs*?

The strength-of-evidence groups that contribute to each evaluation are summarized in Table 2.

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<sup>6</sup> IARC (2019). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: [https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities\\_2020-2024.pdf](https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf).

Table 2. Strength-of-evidence groups used by the *IARC Monographs*

| Evidence of Cancer in Humans          | Evidence of Cancer in Experimental Animals | Mechanistic Evidence                | Evaluation                       |
|---------------------------------------|--|-------------------------------------|----------------------------------|
| Sufficient                            |  |                                     | Carcinogenic (Group 1)           |
|                                       | Sufficient                                 | Strong (exposed humans)             |                                  |
| Limited                               | Sufficient                                 |                                     | Probably carcinogenic (Group 2A) |
| Limited                               |  | Strong                              |                                  |
|                                       | Sufficient                                 | Strong (human cells or tissues)     |                                  |
|                                       |  | Strong (mechanistic class)          | Possibly carcinogenic (Group 2B) |
| Limited                               |  |                                     |                                  |
|                                       | Sufficient                                 |                                     | Not classifiable (Group 3)       |
|                                       |  | Strong                              |                                  |
|                                       | Sufficient                                 | Strong (does not operate in humans) | Not classifiable (Group 3)       |
| All other situations not listed above |  |                                     |                                  |

#### 17. What are the four different categories into which agents are classified by the *IARC Monographs*?

**Group 1:** The agent is *carcinogenic to humans*.

This category is used when there is *sufficient* evidence for cancer in humans. In other words, there is convincing evidence that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing development of cancer in exposed humans. Agents can also be classified in Group 1 on the basis of *sufficient* evidence for cancer in experimental animals supported by *strong* evidence in exposed humans that the agent has mechanistic effects that are important for cancer development.

**Group 2:**

This category includes agents with a range of evidence regarding cancer in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence regarding cancer in humans. At the other extreme are agents for which evidence in humans is not available but for which there is *sufficient* evidence for cancer in experimental animals. There are two subcategories, which indicate different levels of evidence.



**Group 2A:** The agent is *probably carcinogenic to humans*.

This category is used in three different scenarios:

1. When there is *limited* evidence for cancer in humans and *sufficient* evidence for cancer in experimental animals (“*limited* evidence for cancer in humans” means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations, technically termed “chance”, “bias”, or “confounding”, could not be ruled out with reasonable confidence).
2. When there is *limited* evidence for cancer in humans and *strong* mechanistic evidence.
3. When there is *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in human primary cells or tissues.

These scenarios may also occur simultaneously within a Group 2A classification, as was the case for talc (talc reached Group 2A by all three scenarios described above).

**Group 2B:** The agent is *possibly carcinogenic to humans*.

This category is used when there is *limited* evidence for cancer in humans and less-than-sufficient evidence for cancer in experimental animals and less-than-strong mechanistic evidence of key characteristics of carcinogens. This category may also be used when the evidence regarding cancer in humans does not permit a conclusion to be drawn (referred to as *inadequate* evidence) but there is *sufficient* evidence for cancer in experimental animals or *strong* mechanistic evidence.

**Group 3:** The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly when the evidence is *inadequate* regarding cancer in humans and *inadequate* or *limited* for cancer in experimental animals, and mechanistic evidence is less than *strong*. *Limited* evidence for cancer in experimental animals means that the available information suggests a carcinogenic effect but is not conclusive.

**18. How was the evidence reviewed in the IARC Monographs evaluation?**

During an *IARC Monographs* evaluation, experts critically review the scientific evidence according to strict criteria, which focus on determining the strength of the available evidence that the agent causes cancer. These criteria are described in the Preamble to the *IARC Monographs*, which is available on the *IARC Monographs* website: <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

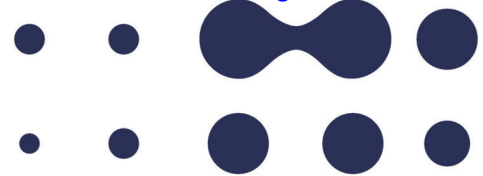
The experts critically review four types of data:

- the situations in which people are exposed to the agent;
- epidemiological studies on cancer in humans exposed to the agent (scientific evidence regarding cancer in humans);
- experimental studies of cancer in laboratory animals treated with the agent (scientific evidence regarding cancer in experimental animals); and
- studies on how cancer develops in response to the agent (scientific evidence on carcinogen mechanisms).

International Agency  
for Research on Cancer



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